IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	:	SAMUEL ROSE, MD
SERIAL NO.	:	08/782,590
FILED	:	January 13, 1997
FOR	:	A METHOD AND COMPOSITION FOR TREATING CANCER BY CONVERTING SOLUBLE RADIOACTIVE TOXIC AGENTS INTO INSOLUBLE RADIOACTIVE TOXIC PRECIPITATES VIA THE ACTION OF NON-MAMMALIAN ENZYMES BOUND TO THE NON-ENDOCYTOSING RECEPTORS OF TARGET CELLS
EXAMINER	:	Susan Ungar Ph.D.
Group Art Unit	:	1640

Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION UNDER 35 U.S.C. 1.132 TRAVERSING GROUNDS OF REJECTION

SIR:

1. I, Alan Epstein, MD, Ph.D., Professor in the Department of Pathology at the University of Southern California, hereby declare that I am a citizen of the United States and a resident of California.

BACKGROUND

2. I received my M.D. degree from Stanford University School of Medicine in 1978 and my Ph.D. in Cancer Biology from Stanford University in 1978. My areas of specialization include

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biochemistry and immunology of nuclear proteins, the production and clinical testing of monoclonal antibodies for the immunodiagnosis and therapy of cancer, and the biological characterization of human malignant lymphomas and leukemias. I am the author of 7 United States Patents and Patent application and have published over 100 articles in the field of cancer therapy and cancer biology.

3. I make this declaration under 37 C.F.R. 1.132 to traverse grounds of rejection of the above-identified U.S. Patent Application, Serial No. 08/782,590 of Samuel Rose, MD (hereinafter the '590 Application).

4. I have examined and am familiar with the original specification, claims, and drawings of the '590 Application; the Official Action mailed March 18, 1998; the Amendment filed September 21, 1998; International Patent Application, Publication number WO 91/09134, having a publication date of June 27, 1991; and the Official Action mailed November 25, 1998.

REGARDING OFFICIAL ACTION MAILED NOVEMBER 25, 1998 PAPER NUMBER 18 (HEREINAFTER "ACTION")

5. Regarding Action, Section 5(a'), pages 3, 4

The method for treating cancer of the invention disclosed by Dr. Rose in his '590 application for treating cancer in its initial step is related to the field of cancer therapy known as antibody dependent prodrug therapy (ADEPT). In ADEPT, the first step of the method calls for the administration of a bispecific reagent having a non-mammalian enzyme moiety. The method of ADEPT further comprises the step of administering a soluble prodrug which is converted into a soluble active drug by the enzyme moiety of the bispecific reagent which is bound to the non-

endocytosing receptors of target cells. The first step of the method of the invention disclosed in th '590 application also calls for the administration of a bispecific reagent having a non-mammalian enzyme moiety. The method of the invention disclosed by Dr. Rose in the '590 application further calls for the administration of a therapeutic agent which is a soluble precipitable material. The therapeutic agent is converted into an insoluble precipitate by the enzyme moiety of the bispecific reagent which is bound to the non-endocytosing receptors of target cells.

The therapeutic effect produced by ADEPT occurs when the soluble active drug diffuses through the tumor tissue and kills neighboring cancer cells. In ADEPT the active drug also diffuses into the systemic circulation where it produces serious systemic toxicity. In contradistinction to ADEPT, as disclosed in the present invention, the therapeutic effect produced is a result of the accumulation and retention of a large amount of the therapeutic agent in its form of an insoluble precipitate which produces a microregion of radiation which kills neighboring cancer cells. Unlike ADEPT which produces serious systemic toxicity when the active drug enters the systemic circulation, the method of the invention disclosed in the '590 application will not produce significant systemic toxicity because the therapeutic agent becomes insoluble and can not diffuse into the systemic circulation.

As disclosed in the '590 application, Dr. Rose's invention comprises a viable therapy for cancer. Given my understanding of the cancer problem and my extensive experience of using radio-labeled antibodies and fragments for therapy, Dr. Rose's soluble precipitable material (the therapeutic agent of the patent application) as disclosed in the invention has great therapeutic potential and can be easily made and tested. It is well known to one skilled in the art that radioactive materials can be used for therapy. In the '590 application Dr. Rose discloses the need to achieve bystander or microregional killing (specification, pages 3-4, 7, and 33-34) by using the therapeutic agent disclosed in the invention. As disclosed in the application and as known to one

skilled in the art, the immobilization of isotopes is therapeutically efficacious and can be achieved by the therapeutic agent disclosed in the invention.

In the '590 application clearly discloses to one skilled in the art that the extracellular insoluble material formed by the soluble precipitable material in the present invention is used to immobilize isotope-carrying molecules and to generate therapeutic radiation fields which kill cancer cells in the immediate microregion. Dr. Rose's application discloses how the soluble isotope-carrying molecule is itself immobilized when it is converted into an insoluble precipitate by the non-mammalian enzyme moiety of the bispecific reagent.

Regarding Action, Section 5(b'), page 4

In view of the long-standing and established field of ADEPT, the information provided in the specification, drawings, and claims of the '590 application enable one skilled in the art to practice the present invention. The therapeutic protocols of the present invention disclose to one skilled in the art the required doses of the therapeutic agent (soluble precipitable material) and the bispecific reagent, is borne out in the long-standing and well-established field of ADEPT and the dosage parameters set forth therein, enable the present invention to be readily practiced without undue experimentation. The international patent application, Publication number WO91/09134, cited in the latest action by the Examiner, recites dosage volumes known to those skilled in the art as far back as the 1991 publication date for administration of bispecific antibodies, of prodrug-activating enzyme, and of prodrugs to adult human patients.

In the '590 application on pages 9-11, Dr. Rose discloses the reasons for the failure of ADEPT therapies which the Examiner quotes in the Action on page 4. The Examiner speculates that the "dosage and methods of administration used in the prior art would not be expected to enable the instant claims." This speculation is not supported by the Examiner since the prior art of ADEPT and the invention disclosed in the '590 application are different. As discussed above, the

method of administration the doses of the prior art of ADEPT can be the same as the invention disclosed in the '590 application, but since the soluble prodrug of the prior art of ADEPT is fundamentally the opposite of the insoluble therapeutic agent of the '590 application, the results will be markedly different. In summary, it is clear to one skilled in the art that the invention disclosed in the '590 application can be readily practiced because the dosage and method have been well-established by the long-standing field of ADEPT. Further it is clear to one skilled in the art that although ADEPT has significant limitations in its efficacy for treating cancer, that the parameters for dosage and method established by the field enable one skilled in the art to practice the present invention.

Regarding Action, Sections 5(c'), 5(d'), page 4

The Examiner raises the question as to the functionality and doses of the bispecific reagent given the obstacles that face antibody-based therapies (impenetrability, uneven distribution, and antigen deficient mutants). As the specification reveals, ADEPT and the present invention have all been designed to overcome the uneven distribution of antibodies in the tumor and the presence of antigen deficient mutants by producing a microregional attack (see discussion above and in specification). Dr. Rose also describes clearly in the specification of the '590 application (page 9-10) that the failure of ADEPT is not a consequence of insufficient bispecific reagent reaching the tumor. In fact, it is quite the opposite. Numerous published papers and my own research in ADEPT-based therapies reveals that sufficient pro-drug is converted in the tumor (i.e. there is enough bispecific reagent in the tumor to convert the prodrug) for therapy. Rather, ADEPT fails because the product of the ADEPT therapy is soluble and diffuses out of the tumor mass into the systemic circulation and produces debilitating systemic toxicity.

Dr. Rose's invention and ADEPT both use the non-mammalian enzymes of previously bound bispecific reagents to convert subsequently administered agents-- the soluble precipitable

material in the present invention and a soluble pro-drug in ADEPT-- for therapy. Essentially, they use the same types bispecific reagents and for both ADEPT and the invention disclosed in the '590 application the bispecific reagent faces the same problems of impermeability of tumors to antibodies, lack of uniform distribution of antibodies, and the presence of antigen deficient mutants. It is well-known to one skilled in the art that the biodistribution of the bispecific reagent is not a limiting factor for ADEPT, and similarly it is known to one skilled in the art that the biodistribution of the bispecific reagent will not preclude the effectiveness of the invention disclosed in the '590 application. Since the bispecific reagent is non-toxic, it is known to one skilled in the art that the dosage of the bispecific reagent can be increased and/or can be given over a long period of time to overcome the obstacles mentioned above.

The vast body of published research in ADEPT includes extensive documentation regarding effective and appropriate doses for the bispecific reagent and the protocols necessary for adjusting the doses under different tumor and patient parameters. Accordingly effective and appropriate dosages and methods of administration are well-know to one skilled in the art and enable Dr. Rose's invention disclosed in the '590 application to be practiced.

Further, it must be noted that required dose levels vary from tumor to tumor and from patient to patient. In both ADEPT and the present invention it is known to one skilled in the art that the dose of the bispecific reagent which is required for therapy varies from patient to patient and depends on many factors such as the size of the tumor, the size of the patient, the location of the tumor, how many cells have been killed, and many other factors. It is not possible to identify any one dose of the administered bispecific reagent which would be suitable in all cases. However, the guidelines for doses have been well-established by research and publications for ADEPT and enable one skilled in the art to practice the invention disclosed in the '590 application.

Regarding Action, Section 5(I'), page 5

The published data in the field of tumor biol gy (in particular the work of Dr. Rakesh Jain of Harvard and my own published data showing the retention of insoluble DNA in tumor tissue) demonstrates that soluble macromolecules and insoluble materials are retained in the extracellular fluid of tumor tissue compared to normal tissue for a longer time and that this prolonged retention in the extracellular fluid of tumor tissue (compared to normal tissue) is a result of the relatively ineffective phagocytic activity of macrophages in tumor tissue and the absence and/or ineffective functioning of lymphatic drainage in tumor tissues. My own data confirms that insoluble DNA relocated to the extracellular fluid is retained for much longer in tumor tissue compared to normal tissue (except the brain). One skilled in the art would readily recognize that the insoluble precipitate formed in Dr. Rose's invention will be retained in the same way. The absence of lymphatics in cancer tissue prevents the rapid transport of macromolecules and insoluble particles into the lymphatics and the to lymph glands from where such material is engulfed by the macrophages lining the sinusoids of the lymph glands.

For the Examiner's consideration, I am including a sample of references showing that there is an impaired or absent lymphatic drainage and impaired macrophages (resulting in reduced or absent phagocytic activity) in tumor tissue. Accordingly it is known to one skilled in the art that in accordance with the inventions disclosed in the '590 application that the insoluble precipitate will remain in the extracellular fluid of tumor tissue for a longer time than in the extracellular fluid of normal tissues.

Regarding Action: Section 8, pages 6, 7

It is well known to one skilled in the art that the attachment of large and/or anionic molecules to a product will make the resultant product cell impermeant. This technique of attaching certain

molecules to products to achieve impermeability has been widely published and is often used where it is desirable to prevent certain chemicals, molecules, or agents from entering cells. The methods of attachment and function of these chemicals is well known to one skilled in the art.

Regarding Action: Section(10), pages 8-9

It is common knowledge in the field of pharmaceutical medicine and oncology that the therapeutic potential and pharmacological action of drugs is a function of their solubility. That is, only when drugs are soluble can they reach, enter, and exhibit their therapeutic effect on cancer cells. A drug does not have a therapeutic affect on cells. In the field of cancer therapy today, all anticancer drugs and cytotoxic agents are soluble. There is no such thing as an insoluble drug.

The invention disclosed in the '590 application comprises the conversion of the therapeutic agent which is a soluble precipitable material into an insoluble precipitate by the non-mammalian enzyme moiety of a previously bound bispecific reagent. The product of the enzymatic conversion is insoluble. In contrast to the invention in Dr. Rose's '590 application, the invention disclosed in the International Patent Application, Publication No. WO 91/109134, comprises the conversion of "an inactive anticancer prodrug into an active type" (page 2, line 10-11). In the International Patent, Publication no. WO 91/109134 and in every example of ADEPT, the product of the enzymatic conversion remains soluble.

For example, the International Patent Application, Publication No. WO 91/109134 (page 9, line 14-20) recites that "any anticancer agent can be used as the original drug for the abovementioned prodrug, but preference is given to those in clinical application such as adriamycin, cisplatin, melphalan, methotrexate, mitomycin C, vincristine, puromycin and phenylenediamine mustard," all of which, when converted by enzyme action as described in the method of the International Patent Application, become soluble active drugs which diffuse through tumor tissue and exhibit their pharmacological action on the neighboring cells.

For one skilled in the art, the specification of the invention disclosed in the '590 application and the extensively studied prior art of ADEPT, clearly demonstrates how the therapeutic agent disclosed in the '590 application is distinct in composition, structure, and function from all of the prodrugs described in the International Patent, Publication No. WO 91/109134. As disclosed in Dr. Rose's '590 application the therapeutic agent is not a function of its solubility because the precipitate formed thereof is insoluble. Rather, the therapeutic potential results from the precipitate being a radioactive molecule. For these reasons the therapeutic agent disclosed in claims 69-83 is distinct from the prior art disclosed in the International Patent, Publication No. WO 91/109134 and from the prior art of ADEPT.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: 5-24-99 Signed: Alan L. Epstein MD, PhD